Boy with autosomal recessive polycystic kidney and autosomal dominant polycystic liver disease

Zingg-Schenk, Andrea ; Caduff, Jürg ; Azzarello-Burri, Silvia ; Bergmann, Carsten ; Drenth, Joost P H ; Neuhaus, Thomas J

Abstract: BACKGROUND Autosomal recessive polycystic kidney disease (ARPKD) shows a great phenotypic variability between patients, ranging from perinatal demise to mildly affected adults. Autosomal dominant polycystic liver disease (PCLD) does not manifest in childhood. CASE-DIAGNOSIS/TREATMENT A boy was reported with the co-occurrence of ARPKD and PCLD. He presented at the age of 16 days with pyelonephritis and urosepsis. Subsequent investigations showed enlarged kidneys and hyperechogenic renal medulla and liver parenchyma. Genetic analysis revealed compound heterozygous mutations in the PKHD1 gene (p.Arg496X and p.Ser1862Leu). After his mother was diagnosed with PCLD, the finding of a liver cyst on ultrasound prompted analysis of the PRKCSH gene, revealing a missense mutation (p.Arg139His). At the most recent follow-up at 13 years of age, the patient's course and clinical examination was uneventful with normal renal and liver function without evidence of portal hypertension. CONCLUSIONS The patient with ARPKD and PCLD has so far demonstrated a benign clinical outcome, consistent with the great phenotypic variability of ARPKD and, apart from the liver cyst, asymptomatic manifestation of PCLD in childhood. However, close long-term follow-up is mandatory.

DOI: https://doi.org/10.1007/s00467-012-2137-5

Pediatr Nephrol (2012) 27:1197–1200
DOI 10.1007/s00467-012-2137-5

BRIEF REPORT

Boy with autosomal recessive polycystic kidney and autosomal dominant polycystic liver disease

Andrea Zingg-Schenk · Jürg Caduff · Silvia Azzarello-Burri · Carsten Bergmann · Joost P. H. Drenth · Thomas J. Neuhaus

Received: 23 October 2011 / Revised: 8 February 2012 / Accepted: 10 February 2012 / Published online: 14 March 2012

Abstract
Background Autosomal recessive polycystic kidney disease (ARPKD) shows a great phenotypic variability between patients, ranging from perinatal demise to mildly affected adults. Autosomal dominant polycystic liver disease (PCLD) does not manifest in childhood.
Case-Diagnosis/Treatment A boy was reported with the co-occurrence of ARPKD and PCLD. He presented at the age of 16 days with pyelonephritis and urosepsis. Subsequent investigations showed enlarged kidneys and hyperechogenic renal medulla and liver parenchyma. Genetic analysis revealed compound heterozygous mutations in the *PKHD1* gene (p.Arg496X and p.Ser1862Leu). After his mother was diagnosed with PCLD, the finding of a liver cyst on ultrasound prompted analysis of the *PRKCSH* gene, revealing a missense mutation (p.Arg139His). At the most recent follow-up at 13 years of age, the patient's course and clinical examination was uneventful with normal renal and liver function without evidence of portal hypertension.
Conclusions The patient with ARPKD and PCLD has so far demonstrated a benign clinical outcome, consistent with the great phenotypic variability of ARPKD and, apart from the liver cyst, asymptomatic manifestation of PCLD in childhood. However, close long-term follow-up is mandatory.

Keywords Autosomal recessive polycystic kidney disease (ARPKD) · Autosomal dominant polycystic liver disease (PCLD) · *PKHD1* gene · *PRKCSH* gene

A. Zingg-Schenk · J. Caduff · T. J. Neuhaus (✉)
Children's Hospital Lucerne,
6000 Lucerne, Switzerland
e-mail: thomas.neuhaus@luks.ch

S. Azzarello-Burri
Institute of Medical Genetics, University Zurich,
Zurich, Switzerland

C. Bergmann
Center for Human Genetics, Bioscientia,
Ingelheim, Germany

C. Bergmann
Department of Human Genetics, RWTH Aachen University,
Aachen, Germany

J. P. H. Drenth
Department of Gastroenterology and Hepatology,
Department of Medicine,
Radboud University Nijmegen Medical Center,
Nijmegen, The Netherlands

Introduction

Autosomal recessive polycystic kidney disease (ARPKD) is caused by mutations in the *PKHD1* gene on chromosome 6p12. There is great phenotypic variability between families, but also within families, ranging from perinatal demise to mildly affected young adults [1, 2]. Patients with ARPKD have hepatic fibrosis with dilated intrahepatic bile ducts, but only rarely develop large liver cysts. Autosomal dominant polycystic liver disease (PCLD) is caused by heterozygous mutations in the *PRKCSH* gene (protein kinase C substrate 80 K-H) on chromosome 19p13 [3] or the *SEC63* gene (SEC63 homolog, *S. cerevisiae*) on chromosome 6q21 [4]. Mutations in these two genes explain about 20–25% of the cases, indicating that at least one other locus is involved in PCLD pathogenesis [5]. PCLD does not manifest in childhood, as liver cysts and clinical symptoms only develop later in adulthood.

ARPKD, PLCD, and autosomal dominant polycystic kidney disease (ADPKD) among others, belong to the group

of ciliopathy diseases. Fibrocystin/polyductin and polycystin-1/2, the products of the genes responsible for ARPKD and ADPKD, are integral membrane proteins in the cilia membrane, whereas glucosidase IIβ and Sec63p, the products of the *PRKCSH* and *SEC63* genes, function in post-translational translocation of proteins into the endoplasmatic reticulum. This case describes the first reported pediatric patient with co-occurrence of ARPKD and PCLD.

Case report

The boy was born prematurely after an uneventful pregnancy at 36 5/7 weeks gestation. He was the only child of non-consanguineous Finnish parents. Birth weight was 2,800 grams and the neonatal course was normal. He presented at the age of 16 days with pyelonephritis and urosepsis (*E. coli*) with full recovery on antibiotic therapy for 14 days (initially gentamicin/amoxicillin, followed by ceftriaxone). Subsequent renal ultrasound showed mildly enlarged kidneys (length 7.4 cm) and hyperechogenic medulla. A micturition cystography demonstrated normal bladder and urethra, excluding vesicoureteric reflux. The further clinical course was uneventful. Ultrasound at the regularly planned follow-up at 9 months of age demonstrated hyperechogenic renal medulla suggestive of nephrocalcinosis and hyperechogenic liver. Renal function, assessed as plasma creatinine, urinary calcium and oxalate excretion, and liver function tests were all normal.

Repeated ultrasound at the age of 2 years showed enlarged kidneys and persistent hyperechogenic renal medulla and liver suggestive of ARPKD prompting further investigations. Genetic analysis revealed compound heterozygous mutations in the *PKHD1* gene (maternally, c.1486C>T/p.Arg496X; paternally: c.5585C>T/p.Ser1862Leu). Ultrasound of the father (at the age of 38 years) showed normal kidneys and liver, whereas the mother's ultrasound (at the age of 37 years) showed normal kidneys, but an abnormal liver (see below). Thus, a diagnosis of ARPKD was made in the boy. Autosomal dominant polycystic kidney disease (ADPKD) appeared to be unlikely as renal parental ultrasound was normal and family history for renal disease was negative. However, as about 2% of ADPKD cases are due to de novo mutations (which were not tested), ADPKD could not be formally ruled out.

When the boy was 7 years old, his mother was diagnosed (at the age of 40 years) with an aneurysm of the anterior cerebral artery, which was successfully clipped. Subsequent investigations showed multiple liver cysts, but again normal renal ultrasound and renal function. Family history revealed that the maternal grandmother also had liver cysts. The suggested diagnosis of PCLD was confirmed by genetic analysis showing a missense mutation in exon 6 of the *PRKCSH* gene (c.416G>A; p.Arg139His) [6]. The mother died at the age of 45 years of septicemia.

The boy's further course was uneventful with normal somatic and cognitive development. Repeated ultrasound showed persistent hyperechogenicity of both the renal medulla and the liver. At the age of 9 years, a small cyst was detected in the liver segment IV (Fig. 1), suggestive of PCLD. Genetic analysis of the *PRKCSH* gene showed the maternal mutation, confirming the diagnosis of PCLD.

At the most recent follow-up at the age of 13 years, the boy was—apart from seasonal allergic pollinosis—asymptomatic. His clinical examination was uneventful. Renal and liver function, full blood count, urinalysis, and blood pressure were normal. In addition, echocardiography and cerebral MRI—performed to detect mitral valve prolapse or cerebral aneurysm—showed normal findings. Ultrasound of the liver and kidneys demonstrated persistent hyperechogenicity of the liver and renal medulla and normal-sized right (length 9.5 cm), but enlarged left kidney (10.5 cm). There was no evidence of portal hypertension or splenomegaly. So far, the patient has not been given any medication.

Discussion

This report describes a male patient with the combination of two rare diseases, ARPKD and PCLD, genetic analysis confirming the clinical diagnosis. Ultrasound findings of

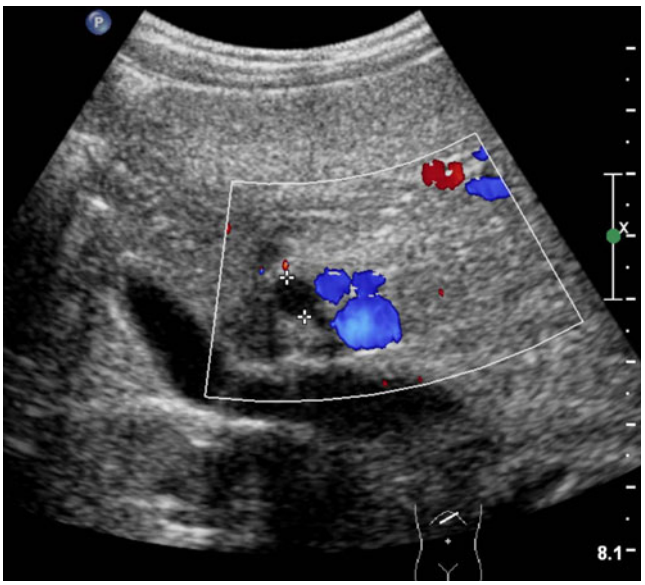

Fig. 1 Sonography of the liver at the age of 9 years. A small cyst adjacent to hepatic vessels (located in segment IV); parenchyma with slightly hyperechogenic and nodular structure

kidneys and liver were consistent with ARPKD, but no liver biopsy was performed to verify hepatic fibrosis. There should be little doubt about the pathogenicity of the two mutations in the *PKHD1* gene (c.1486C>T/p.Arg496X and c.5585C>T/p.Ser1862Leu). The truncating change on the maternal allele represents the most frequent Finnish *PKHD1* founder mutation. The missense mutation detected on the paternal allele was not present in 400 control chromosomes, affects an evolutionarily conserved amino acid and was predicted in silico by different bioinformatic tools used (AlignGVGD, SIFT, PolyPhen2, and PMut) to be of pathogenic relevance.

Repeated ultrasound revealed a liver cyst at young age (9 years), unusual for both ARPKD and PCLD as cysts in PCLD usually only develop in adulthood. However, it can not be ruled out that the cystic structure might mimic a dilated hepatic duct as in ARPKD.

The main clinical issue for this child with co-occurrence of both ARPKD and PCLD is the concern that the combination will lead to earlier clinical presentation and poor(er) outcome. Whereas ARPKD carries substantial morbidity and mortality among infants and children, PCLD is asymptomatic during childhood. So far, the patient's clinical course with ARPKD and PCLD has been—apart from the neonatal urosepsis—uneventful. Extensive investigations, including repeated assessments of renal and liver function, echocardiography, and cerebral MRI, were normal.

ARPKD is caused by mutations in the *PKHD1* gene and occurs with a proposed incidence of 1:20,000 [1]. Principal histologic manifestations involve both the kidneys and the liver, with dilation of renal collecting ducts and distal tubuli as well as dysgenesis of the hepatic portal triad known as ductal plate malformation. Renal ultrasound shows enlarged kidneys with hyperechogenic parenchyma and small cysts. The hepatobiliary findings include hyperechogenic liver parenchyma and dilated intrahepatic bile ducts (Caroli syndrome), but usually no large liver cysts. There is great phenotypic variability between families, but also within families, ranging from perinatal demise to mildly affected adults [1, 2]. The 1- and 10-year survival rates are 85 and 82%, respectively. Chronic renal failure is first detected at a mean of 4 years, and renal survival rates (defined as start of renal replacement therapy or death due to end-stage renal failure) are 86, 71, and 42% at 5, 10, and 20 years, respectively [1]. Sequelae of congenital hepatic fibrosis and portal hypertension occur in almost half of patients. A positive correlation can be demonstrated between renal and hepatobiliary morbidity [1].

Fibropolycystic liver diseases in children include hepatic fibrosis/ARPKD as well as biliary hamartoma, choledochal cysts and PCLD [7]. Autosomal dominant PCLD is a distinct entity of cotranslational protein processing [8] caused by a mutation in either the *PRKCSH* gene [3] or the *SEC63* gene [4], with a prevalence of 1:150,000. The cysts probably arise from biliary microhamartomas and have no connection to the biliary tree. Liver structure is unchanged, and hepatic fibrosis is absent in liver biopsy specimens or explanted livers [9]. Liver function remains normal in most patients and kidney function is not affected. PCLD is generally a mild disease and symptoms develop only later in adulthood, mainly due to increased intra-abdominal pressure caused by large liver cysts. Usually, women tend to present more and larger cysts than men. Mitral valve abnormalities are common (20%); some patients have inguinal hernia, colonic diverticula, and gallstones, whereas only a few develop cerebral aneurysms (4%) [10].

A further cause of liver cysts in adults is ADPKD. The occurrence of liver cysts is related to renal function and age: the majority of patients above 40 years of age have liver cysts on ultrasound, in contrast to none below 10 years [11].

ARPKD, ADPKD, and PCLD are ciliopathies. Thus, questions arise as to whether ARPKD and PCLD share a common pathway and whether their co-occurrence might lead to earlier development of cysts and poorer clinical outcome. In fact, Fedeles et al. have recently shown a genetic interaction network of five genes for human polycystic kidney and liver diseases in mice [12]. The genes *PRKCSH* and *SEC63* and their respective gene products glucosidase IIβ and Sec63p function in protein translocation and quality control pathways in the endoplasmatic reticulum. Glucosidase IIβ and Sec63p are required for adequate expression of a functional complex of the ADPKD gene products polycystin-1 and polycystin-2, with polycystin-1 being the rate-limiting component. In addition, fibrocystin/polyductin (the product of the gene *PKHD1*) is an endoplasmatic reticulum-passing transmembrane protein, thus a client protein for glucosidase IIβ and Sec63p. Fedeles et al. have shown that inactivation of *SEC63* in mice with ARPKD led to more severe cystic disease. Their interpretation was that co-occurrence of PCLD and ARPKD led to reduced dosage of polycystin-1, which sensitized kidney tubules and bile ducts to expression of more severe cystic phenotypes resulting from alterations in fibrocystin/polyductin [12].

These data suggest that patients with co-occurrence of ARPKD and PLCD are at risk of earlier development of both kidney and liver cysts with subsequent poorer outcome. However, the observation of the long-term course of our patient suggests a discordant clinical pattern with a mild renal phenotype of ARPKD and an early occurrence of a liver cyst in PCLD. Thus, close long-term follow-up is mandatory.

References

1. Bergmann C, Senderek J, Windelen E, Küpper F, Middledorf I, Schneider F, Dornia C, Rudnik-Schöneborn S, Konrad M, Schmitt CP, Seeman T Neuhaus TJ, Vester U, Kirfel J, Büttner R, Zerres K and members of the APN (2005) Clinical consequences of PKHD1 mutations in 164 patients with autosomal recessive polycystic disease (ARPKD). Kidney Int 67:829–848
2. Rossetti S, Harris PC (2007) Genotype-phenotype correlations in autosomal dominant and autosomal recessive polycystic kidney disease. J Am Soc Nephrol 18:1378–1380
3. Drenth JP, te Morsche RH, Smink R, Bonifacino JS, Jansen JB (2003) Germline mutations in PRKCSH are associated with autosomal dominant polycystic liver disease. Nat Genet 33:345–347
4. Davila S, Furu L, Gharav AG, Tian X, Onoe T, Qian Q, Li A, Cai Y, Kamath PS, King BF, Azurmendi PJ, Tahvanainen P, Kääriänen H, Köckerstedt K, Devuyst O, Pirson Y, Martin RS, Lifton RP, Tahvanainen E, Torres VE, Somlo S (2004) Mutations in SEC63 cause autosomal dominant polycystic liver disease. Nat Genet 36:575–577
5. Waanders E, Venselaar H, te Morsche RH, de Koning DB, Kamath PS, Torres VE, Somlo S, Drenth JP (2010) Secondary and tertiary structure modeling reveals effects of novel mutations in polycystic liver disease genes PRKCSH and SEC63. Clin Genet 78:47–56
6. Waanders E, Te Morsche RH, de Man RA, Jansen JB, Drenth JP (2006) Extensive mutational analysis of PRKCSH and SEC63 broadens the spectrum of polycystic liver disease. Hum Mutation 27:830
7. Veigel MC, Prescott-Focht J, Rodriguez MG, Zinati R, Shao L, Moore CAW, Lowe LH (2009) Fibropolycystic liver disease in children. Pediatr Radiol 39:317–327
8. Drenth JP, Martina JA, van de Kerkhof R, Bonifacino JS, Jansen JB (2005) Polycystic liver disease is disorder of cotranslational protein processing. Trends Mol Med 11:37–42
9. Qian Q, Li A, King BF, Kamath PS, Lager DJ, Huston J, Shub C, Davila S, Somlo S, Torres VE (2003) Clinical profile of autosomal dominant polycystic liver disease. Hepatology 37:164–171
10. Tahvanainen E, Tahvanainen P, Kääriäinen H, Höckerstedt K (2005) Polycystic liver and kidney diseases. Ann Med 37:546–555
11. Nicolau C, Torra R, Bianchi L, Vilana R, Gilabert R, Darnell A, Bru C (2000) Abdominal sonographic study of autosomal dominant polycystic kidney disease. J Clin Ultrasound 28:277–282
12. Fedeles SV, Tian X, Gallagher AR, Mitobe M, Nishio S, Lee SH, Cai Y, Geng L, Crews CM, Somlo S (2011) A genetic interaction network of five genes for human polycystic kidney and liver diseases defines polycystin -1 as the central determinant of cyst formation. Nat Genet 43:639–647